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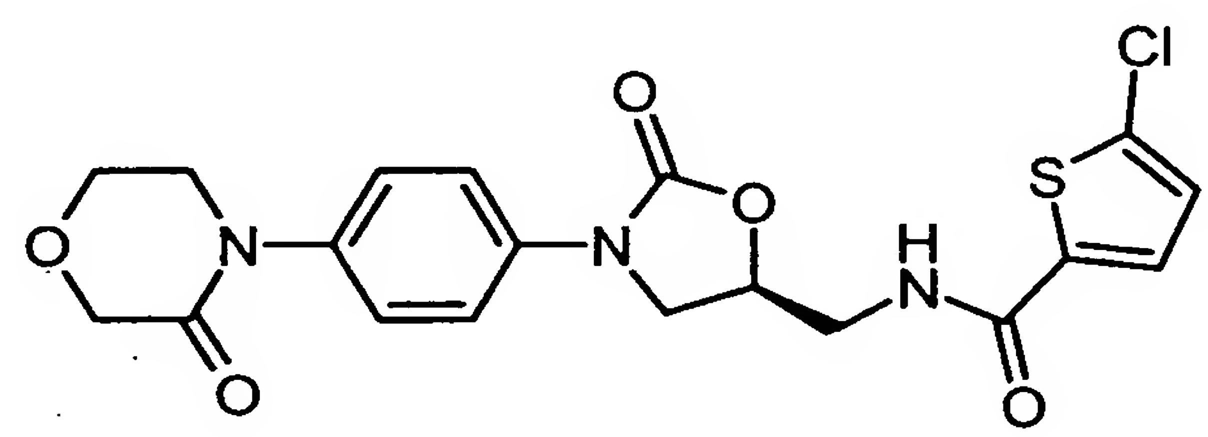
Method for producing 5-chloro-*N*-({(5*S*)-2-oxo-3-[4-(3-oxo-4-morpholinyl)phenyl]-1,3-oxazolidin-5-yl}methyl)-2-thiophenecarboxamide

The present invention relates to a process for preparing 5-chloro-*N*-({(5*S*)-2-oxo-3-[4-(3-oxo-4-morpholinyl)phenyl]-1,3-oxazolidin-5-yl}methyl)-2-thiophene-carboxamide starting from 5-chlorothiophene-2-carbonyl chloride, (2*S*)-3-aminopropane-1,2-diol and 4-(4-aminophenyl)-3-morpholinone.

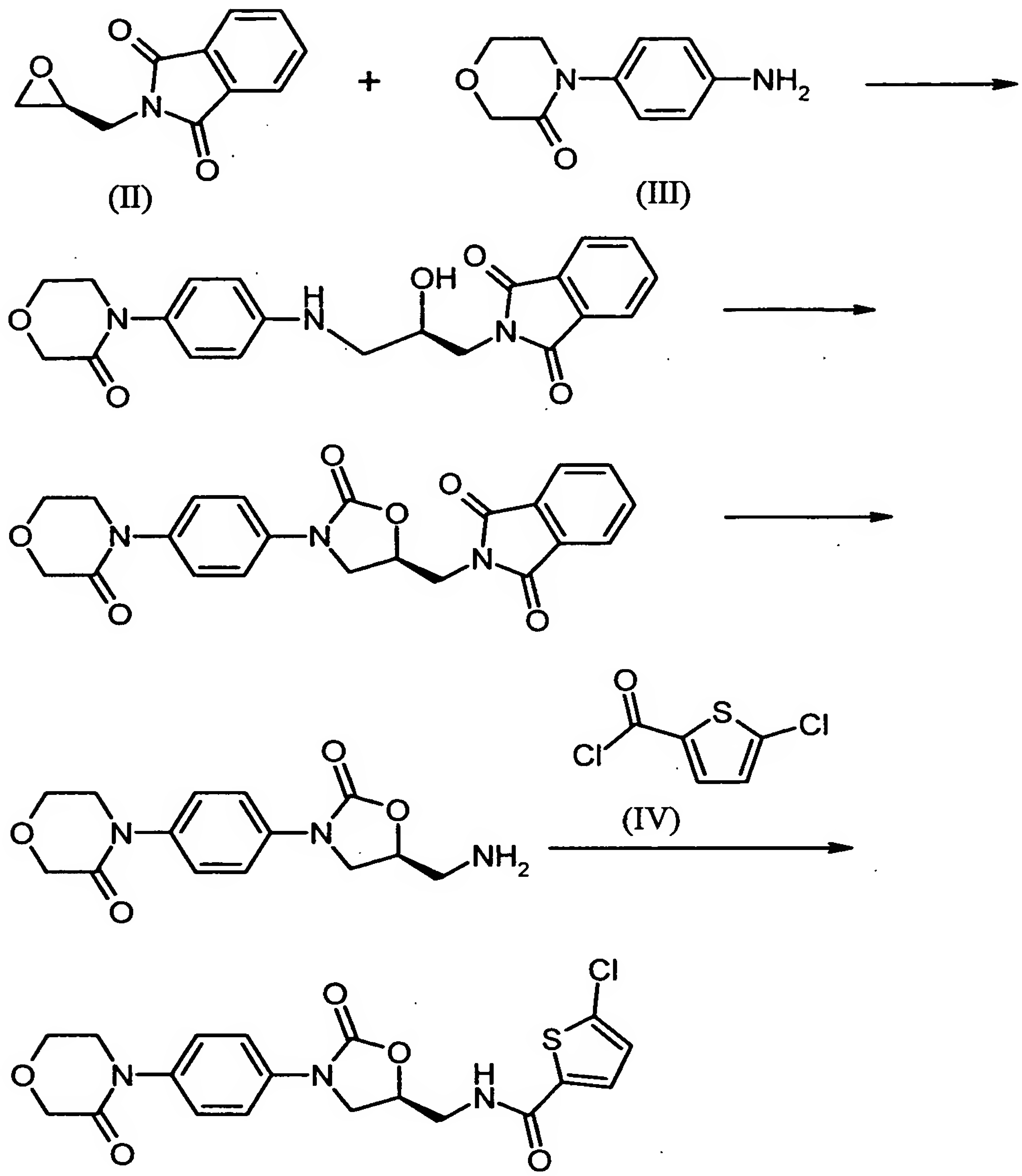
The compound 5-chloro-*N*-({(5*S*)-2-oxo-3-[4-(3-oxo-4-morpholinyl)phenyl]-1,3-oxazolidin-5-yl}methyl)-2-thiophenecarboxamide is known from WO-A 01/47919 and corresponds to the formula (I)



(I).

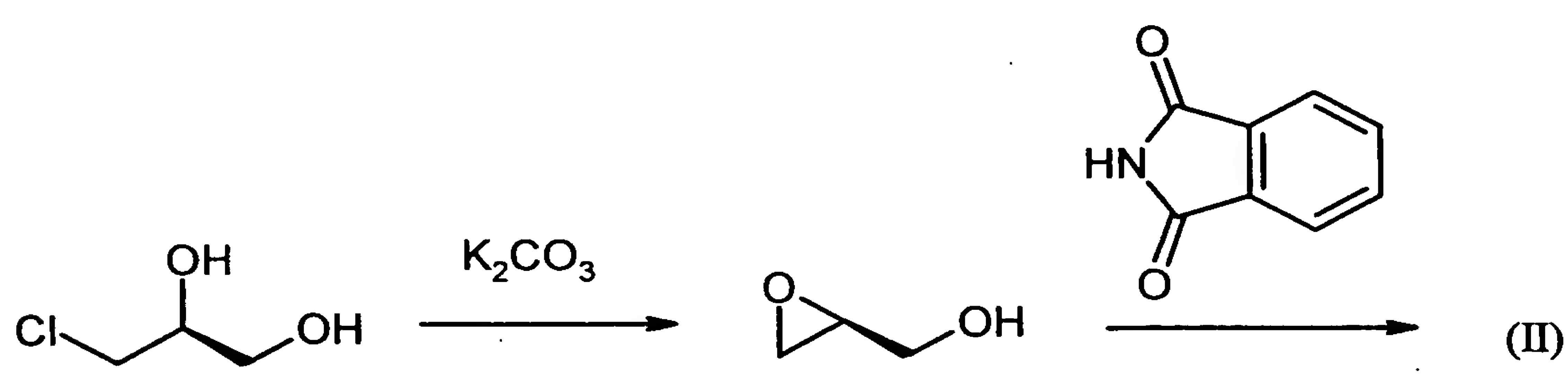
The compound of the formula (I) acts as an inhibitor of clotting factor Xa and may be used as an agent for the prophylaxis and/or treatment of thromboembolic disorders, especially myocardial infarction, angina pectoris (including unstable angina), reocclusions and restenoses after angioplasty or aortocoronary bypass, stroke, transient ischemic attacks, peripheral arterial occlusive diseases, pulmonary embolisms or deep venous thromboses.

WO-A 01/47919 also describes a method for preparing the compound of the formula (I) starting from 2-[(2*S*)-2-oxiranylmethyl]-1*H*-isoindole-1,3(2*H*)-dione (II), 4-(4-aminophenyl)-3-morpholinone (III) and 5-chlorothiophene-2-carbonyl chloride (IV):



(I)

In this method, the epoxyphthalimide (II) is prepared by reacting (2*S*)-1-chloropropane-2,3-diol (V) with potassium carbonate via the stage of (*S*)-glycidol (VI) and subsequent Mitsunobu reaction with phthalimide:



(V) (VI)

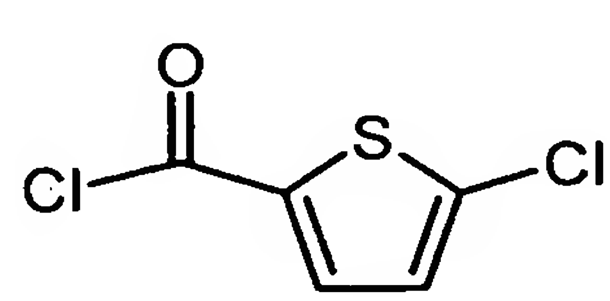
The process known from WO-A 01/47919 has various disadvantages which have a particularly unfavorable effect when the compound of the formula (I) is prepared on the industrial scale:

For instance, the glycidol (VI), especially in relatively large amounts, is polymerization-sensitive and thus not storage-stable, additionally toxic and potentially carcinogenic. The Mitsunobu reaction in the preparation of compound (II) is technically costly and inconvenient, one reason being that racemization occurs readily in relatively large batches. Another reason is that the atom economy is extremely unsatisfactory, since triphenylphosphine oxide and diisopropyl azodicarboxylate hydrazide are generated in stoichiometric amounts as waste materials. In addition, the nitrogen atom in the oxazolidinone ring of the target molecule (I) is introduced in phthalimide-protected form. However, the phthalic acid radical as a protecting group has to be removed in the further course of the synthesis, which means an increase in the number of stages and additional waste.

It is thus an object of the present invention to provide a simplified process for preparing the compound of the formula (I) in large amounts.

It has been found that, surprisingly, the compound of the formula (I) can be prepared in improved yield in a shortened reaction sequence using storage-stable and less toxic starting materials, starting from 5-chlorothiophene-2-carbonyl chloride (IV), (2*S*)-3-aminopropane-1,2-diol hydrochloride (VII) and 4-(4-aminophenyl)-3-morpholinone (III). In this reaction sequence, the use of protecting groups is also avoided, which reduces the number of stages and thus shortens the reaction time.

In the first step of the process according to the invention, 5-chlorothiophene-2-carbonyl chloride (IV)

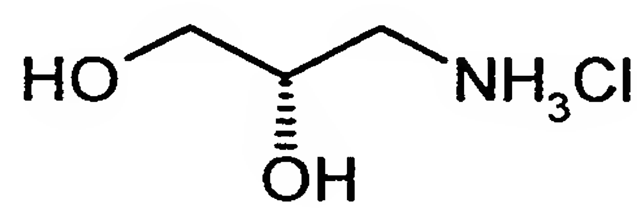


(IV)

is prepared from 5-chlorothiophene-2-carboxylic acid.

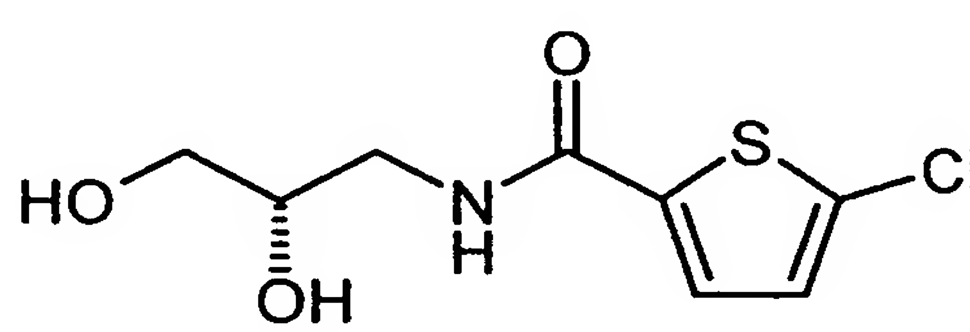
Compound (IV) may be prepared under the customary reaction conditions for the preparation of carbonyl chlorides from the corresponding carboxylic acids. Preference is given to the reaction of 5-chlorothiophene-2-carboxylic acid with thionyl chloride as the chlorinating reagent in toluene as the solvent.

In the second step of the process according to the invention, 5-chlorothiophene-2-carbonyl chloride (IV) is reacted with (2*S*)-3-aminopropane-1,2-diol hydrochloride (VII)



(VII)

to give N-((*S*)-2,3-dihydroxypropyl)-5-chlorothiophene-2-carboxamide (VIII)

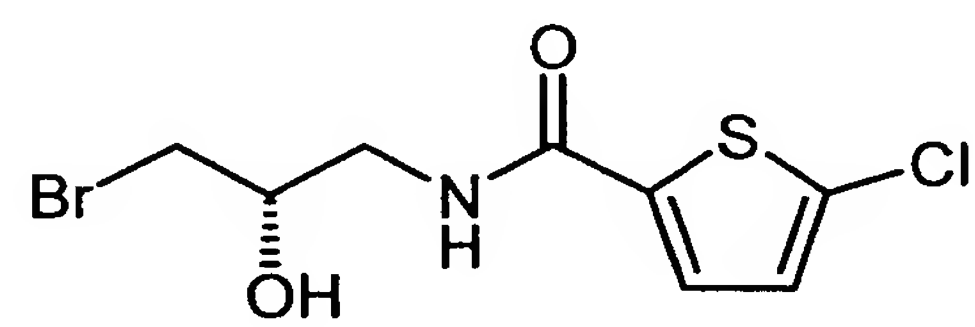


(VIII).

The reaction (IV) + (VII) -> (VIII) may be effected under the reaction conditions customary for the formation of amide bonds from the appropriate carbonyl chlorides and amines. Preference is given to a biphasic system composed of aqueous sodium hydrogencarbonate solution and 2-methyltetrahydrofuran as the organic solvent. (2*S*)-3-Aminopropane-1,2-diol is used in the form of the free base or in the form of the acid addition salt. Preference is given to the hydrochloride (VII) which crystallizes better than the free base and can therefore be handled readily. To increase the reaction yield, optionally either an excess of amine is used or an auxiliary base is added. The addition of from 1 to 3, preferably 2, equivalents of an auxiliary base such as sodium hydrogencarbonate is preferred. The reaction is

effected generally within a temperature range of from 0°C to 40°C, preferably of from 5°C to 30°C.

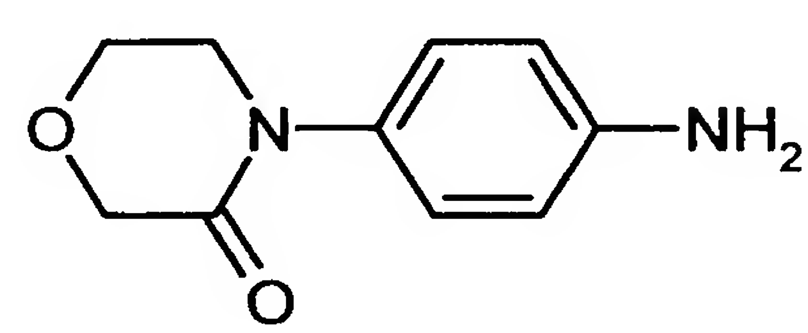
In the third step of the process according to the invention, N-((*S*)-2,3-dihydroxypropyl)-5-chlorothiophene-2-carboxamide (VIII) is converted to N-((*S*)-3-bromo-2-hydroxypropyl)-5-chlorothiophene-2-carboxamide (IX)



(IX).

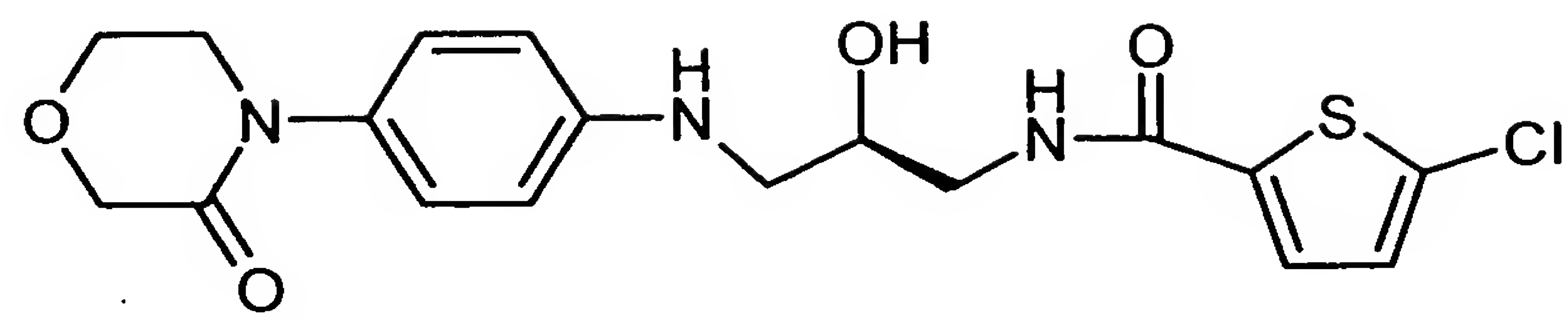
The reaction (VIII) -> (IX) is carried out with from 1 to 5, preferably from 3 to 5, in particular 4, equivalents of a solution of hydrobromic acid in acetic acid, optionally in the presence of acetic anhydride. The reaction temperature is between 20°C and 80°C, preferably between 60 and 65°C. The amount of methanol added may be varied over a wide range; preference is given to using from 40 to 80 mol, in particular from 50 to 60 mol, of methanol per mole of (VIII). For the workup, the solvents are distilled off, preferably under reduced pressure. The remaining distillation residue is optionally also neutralized before the filtration of the product.

In the fourth step of the process according to the invention, N-((*S*)-3-bromo-2-hydroxypropyl)-5-chlorothiophene-2-carboxamide (IX) is reacted with 4-(4-aminophenyl)-3-morpholinone (III)



(III)

to give N-{(*R*)-2-hydroxy-3-[4-(3-oxomorpholin-4-yl)phenylamino]propyl}-5-chlorothiophene-2-carboxamide (X)



(X).

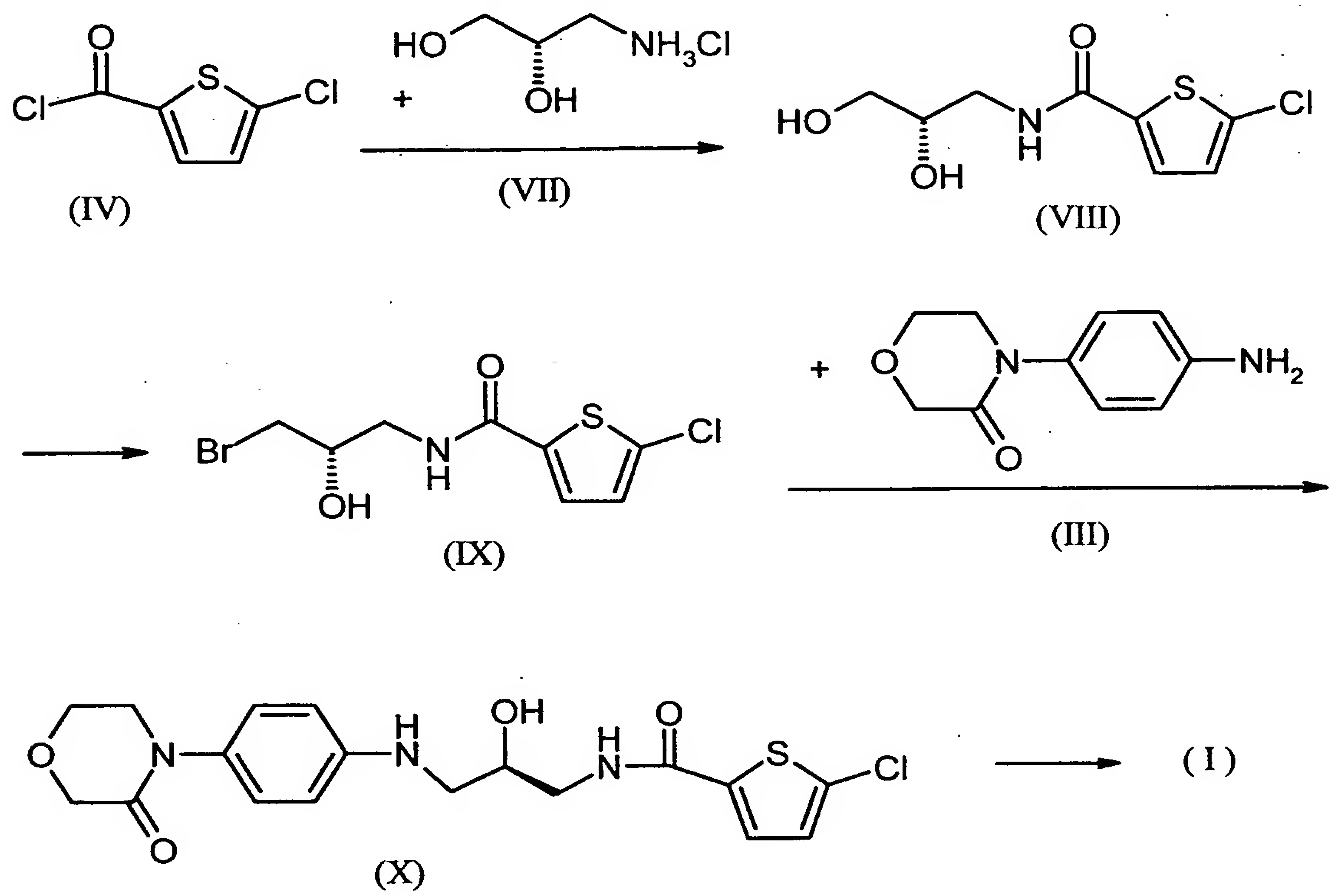
The solvent for the reaction (IX) + (III) -> (X) may be varied widely; preference is given to toluene. The reaction temperature is between 80°C and 200°C; preference is given to a range between 90°C and 110°C. The reaction is effected optionally in the presence of an auxiliary base, for example triethylamine, diisopropylethylamine or collidine; preference is given to using collidine. The stoichiometry of the reaction and the reaction time are variable over a wide range; preference is given to a ratio of compound (IX) to compound (III) to collidine of 1.2 to 1.0 to 1.0 and a reaction time of from 4 to 8 hours, especially of from 5 to 6 hours.

In the fifth step of the process according to the invention, N-{(*R*)-2-hydroxy-3-[4-(3-oxomorpholin-4-yl)phenylamino]propyl}-5-chlorothiophene-2-carboxamide (X) is reacted with phosgene or a phosgene equivalent to give 5-chloro-*N*-({(5*S*)-2-oxo-3-[4-(3-oxo-4-morpholinyl)phenyl]-1,3-oxazolidin-5-yl}methyl)-2-thiophene-carboxamide (I).

In the reaction (X) -> (I), one or more equivalents of phosgene or phosgene equivalents are used in the presence of inert solvents or solvent mixtures. Phosgene equivalents are, for example, phosgene replacements such as di- or triphosgene, or carbon monoxide equivalents, for example N,N-carbonylbisimidazole. Preference is given to using from 1 to 2 equivalents, in particular from 1.1 to 1.3 equivalents, of N,N-carbonylbisimidazole in a solvent mixture of 1-methyl-2-pyrrolidone and toluene. For purification of the product, a clarifying filtration and/or a recrystallization optionally follows. The reaction is effected generally within a temperature range of from 20°C to 150°C, preferably of from 30°C to 110°C, in particular of from 75°C to 85°C.

The individual stages of the process according to the invention may be carried out at standard, elevated or at reduced pressure (for example of from 0.5 to 5 bar). In general, standard pressure is used.

The following scheme summarizes the synthesis:



The invention is illustrated in detail below by a preferred working example, to which it is not, however, restricted. Unless stated otherwise, all quantitative data relates to percentages by weight.

Synthesis of 5-chloro-*N*-({(5*S*)-2-oxo-3-[4-(3-oxo-4-morpholinyl)phenyl]-1,3-oxazolidin-5-yl}methyl)-2-thiophenecarboxamide (I)

1st step:

5-Chlorothiophene-2-carbonyl chloride (IV)

53.6 g of 5-chlorothiophene-2-carboxylic acid (commercially available) are suspended in 344 g of toluene and heated to 80°C. At this temperature, 47.2 g of

thionyl chloride are added dropwise over a period of 20 minutes, then the mixture is stirred at from 75 to 80°C for 30 minutes and then at reflux temperature for two hours until completion of gas evolution. After cooling, the reaction mixture is concentrated to a volume of approx. 200 ml at from 30 to 35°C and a pressure of from 40 to 48 mbar. The thus obtained solution of the acid chloride in toluene is reacted directly in the next stage.

2nd step:

N-((*S*)-2,3-Dihydroxypropyl)-5-chlorothiophene-2-carboxamide (VIII)

461 g of sodium hydrogencarbonate and 350 g of (2*S*)-3-aminopropane-1,2-diol hydrochloride (VII) (commercially available) are initially charged at from 13 to 15°C in 2.1 l of water and admixed with 950 ml of 2-methyltetrahydrofuran. 535.3 g of 5-chlorothiophene-2-carbonyl chloride (approx. 93%) in 180 ml of toluene are added dropwise to this mixture with cooling at from 15 to 18°C over a period of two hours. For workup, the phases are separated and the organic phase is admixed in several steps with a total of 1.5 l of toluene. The precipitated product is filtered off with suction, washed with ethyl acetate and dried.

Yield: 593.8 g; corresponds to 91.8% of theory.
Melting point: 114 to 114.5°C

3rd step:

N-((*S*)-3-Bromo-2-hydroxypropyl)-5-chlorothiophene-2-carboxamide (IX)

301.7 ml of a 33% solution of hydrobromic acid in acetic acid are added to a suspension of 100 g of N-((*S*)-2,3-dihydroxypropyl)-5-chlorothiophene-2-carboxamide (VIII) in 250 ml of glacial acetic acid at from 21 to 26°C over a period of 30 minutes. Subsequently, 40 ml of acetic anhydride are added and the reaction mixture is stirred at from 60 to 65°C for three hours. At 20 to 25°C, 960 ml of methanol are then added over a period of 30 minutes. The reaction mixture is stirred under reflux for 2.5 hours and then overnight at from 20 to 25°C. For workup, the solvents are distilled off under reduced pressure at approx. 95 mbar. The remaining

suspension is admixed with 50 ml of 1-butanol and 350 ml of water. The precipitated product is filtered off with suction, washed with water and dried.

Yield: 89.8 g; corresponds to 70.9% of theory.
Melting point: 120°C

4th step:
N-{(*R*)-2-Hydroxy-3-[4-(3-oxomorpholin-4-yl)phenylamino]propyl}-5-chloro-thiophene-2-carboxamide (X)

55 g of N-((*S*)-3-bromo-2-hydroxypropyl)-5-chlorothiophene-2-carboxamide (IX) and 29.4 g of 4-(4-aminophenyl)-3-morpholinone (III) (a preparation method is described, for example, in WO-A 01/47919 on pages 55 to 57) are suspended at from 20 to 25°C in 500 ml of toluene and admixed with 18.5 g of collidine and 10 ml of ethanol. The reaction mixture is heated to from 103 to 105°C for 6 hours and then admixed while hot with 50 ml of 1-butanol. After cooling to 30°C, the precipitated reaction product is filtered off with suction, washed with toluene and water and dried.

Yield: 42.0 g; corresponds to 61.8% of theory.
Melting point: 198.5°C

5th step:
5-Chloro-*N*-({(5*S*)-2-oxo-3-[4-(3-oxo-4-morpholinyl)phenyl]-1,3-oxazolidin-5-yl}methyl)-2-thiophenecarboxamide (I)

25 g of N-{(*R*)-2-hydroxy-3-[4-(3-oxomorpholin-4-yl)phenylamino]propyl}-5-chlorothiophene-2-carboxamide (X) are suspended at from 20 to 25°C in 250 ml of toluene and admixed with 37.5 ml of 1-methyl-2-pyrrolidone and 11.9 g of N,N-carbonyldiimidazole. The reaction mixture is heated to from 80 to 83°C for 20 minutes and subsequently heated to 115°C for one hour. After cooling to 20°C, the precipitated reaction product is filtered off with suction, washed twice with 25 ml each time of water and dried at 60°C under reduced pressure.

Yield: 23.7 g; corresponds to 91.5% of theory.

Melting point: 230°C